

### **Remarks**

Applicants respectfully request that the present remarks be entered and made of record in the instant application.

#### ***I. Claims***

Upon entry of the foregoing amendment, claims 55, 76, 78-87, and 89-98 are pending in the application, with claims 55, 76 and 87 being the independent claims. Claims 77 and 88 are sought to be canceled. Claims 76 and 84-87 are sought to be amended. It is respectfully requested that the amendments be considered and entered. Applicants note that the claims as presented herein are directed to cell culture media and methods for expanding CD34+ hematopoietic cells in culture media containing N-acetyl-L-cysteine and serum albumin.

#### ***II. Rejection of the Claims Under 35 U.S.C. § 103(a)***

Claims 55 and 76-98 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Smith *et al.* (WO 95/06112) in view of Darfler (U.S. Patent No. 4,927,762) in light of Walsh *et al.* (*J. Clin. Invest.*, 94:1440-1448, 1994) and Hamilton *et al.* (WO 93/20195). (Office Action, page 4.) Applicants respectfully disagree but have amended claims to facilitate prosecution.

As Applicants understand, the Examiner asserts that by combining the disclosures of Smith *et al.*, Darfler, Walsh *et al.* and Hamilton *et al.*, one of skill in the art would arrive at the claimed invention. (Office Action, page 4.) The U.S. Supreme Court recently noted that:

A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, *it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.* This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

(*KSR Int'l v. Teleflex Inc.*, 550 U.S. at \_\_, Slip Op. at 1-24 (Apr. 30, 2007) (No. 04-1350) (emphasis added).) Thus, the U.S. Supreme Court has provided guidance for assessing whether an

invention is obvious and has indicated that merely collecting “building blocks” does not provide a reason that would prompt one of skill in the art to arrive at the claimed invention.

The Examiner cites Smith *et al.* as discussing a method of expanding human CD34+ hematopoietic cells in suspension culture using a serum free medium comprising amino acids, cytokines, growth factors and hydrocortisone. (Office Action, pages 4-5.) The Examiner acknowledges that Smith *et al.* does not teach the use of N-acetyl-cysteine in the culture medium and cites Darfler as discussing the use of this compound with lymphoid cells.

Applicants have amended independent claims 76 and 87 to recite a method for expanding CD34+ hematopoietic cells comprising contacting the CD34+ hematopoietic cells with a serum free medium “comprising N-acetyl-cysteine and serum albumin.” Applicants note that Darfler discusses the use of antioxidant compounds such as N-acetyl-L-cysteine for culturing lymphoid cells in serum free media lacking albumin. (See eg., Darfler at column 6, line 66 through column 7, line 4.) Darfler also discusses that the stability of N-acetyl-L-cysteine is improved in the absence of albumin. (Darfler, column 6, lines 24-31.) Further, the lymphoid cells Darfler discusses are hybridoma cells, not CD34+ positive hematopoietic cells. The presence of the CD34 antigen on the surface of a cell serves as a marker of hematopoietic stem cells (page 3, lines 4-5 of the specification) not mature lymphocytes such as hybridoma cells. One skilled in the art would not expect the growth requirements of a mature lymphocyte to necessarily be the same as those for a hematopoietic stem cell. Therefore, one skilled in the art would have no reason to combine Darfler with Smith *et al.* to arrive at the claimed compositions and methods because Darfler discusses the use of N-acetyl-L-cysteine in the absence of albumin and culturing a different cell type. Without such a reason for combining Smith *et al.* with Darfler, a *prima facie* case of obviousness has not been established.

The Examiner further cites Walsh *et al.* and Hamilton *et al.* as discussing the use of recombinant techniques with hematopoietic cells. (Office Action, page 6.) However, Walsh *et al.* discusses culturing CD34+ cells in media containing serum. (Walsh *et al.*, page 1442, column 1, first full paragraph.) Hamilton *et al.* also discusses the culture of recombinant lymphoid cells in the presence of serum but makes no reference to CD34+ lymphoid cells. (Hamilton *et al.*, page 18, line 21.) Given that both Walsh *et al.* and Hamilton *et al.* discuss culturing lymphoid cells in the

presence of serum and that Hamilton *et al.* does not teach CD34+ cells at all, it is not clear how one skilled in the art would arrive at the claimed compositions and methods for the culture of recombinant CD34+ hematopoietic cells in a serum free media by combining these references with Smith *et al.* and Darfler. Without a rationale of how these references could be combined to arrive at the claimed invention, a *prima facie* case of obviousness has not been established.

In addition, the Examiner asserts that the limitation “the recombinant CD34+ hematopoietic cells” does not affect the patentability of the claimed composition or method because it is present in the preamble of the claim. (Office Action, pages 6-7.) Applicants believe that the recitation of the phrase “the cells” in the body of the claim 76 is a clear reference to the “recombinant CD34+ cells” in the preamble. However, to facilitate prosecution and to make this point clear, Applicants have amended claims 76 and 84-86 to recite specifically “recombinant CD34+ cells” in the body of the claim. Applicants believe these amendments address the Examiner’s concerns.

In summary, Applicants assert that the Examiner has not provided a reason why one skilled in the art would combine the four cited references to arrive at compositions and methods for the culture of recombinant CD34+ cells in serum free media. Absent such a reason, a *prima facie* case of obviousness has not been established.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 103(a).

***Conclusion***

Applicants believe that a full and complete Reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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